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Diagnosis and Treatment of Type 2 Diabetes in Adults
A Review

Rita R. Kalyani, MD, MHS; Joshua J. Neumiller, PharmD, CDCES; Nisa M. Maruthur, MD, MHS; Deborah J. Wexler, MD, MSc

IMPORTANCE Type 2 diabetes involves progressive loss of insulin secretion from pancreatic β cells in the setting of insulin resistance and manifests clinically as hyperglycemia. Type 2 diabetes accounts for 90% to 95% of all cases of diabetes globally, with estimates ranging from 589 million to 828 million people worldwide. In the US, type 2 diabetes affects approximately 1 in 6 adults.

OBSERVATIONS Risk factors for type 2 diabetes include older age, family history, overweight or obesity, physical inactivity, gestational diabetes, Hispanic ethnicity, and American Indian or Alaska Native, Asian, or Black race. Diabetes is diagnosed if fasting plasma glucose is greater than or equal to 126 mg/dL, hemoglobin A_{1C} is greater than or equal to 6.5%, or 2-hour glucose during 75-g oral glucose tolerance testing is greater than or equal to 200 mg/dL. Approximately one-third of adults with type 2 diabetes have cardiovascular disease and 10.1% have severe vision difficulty or blindness. The prevalence of type 2 diabetes is 39.2% among patients with kidney failure. Although weight management is an important component of treatment for type 2 diabetes, no specific diet has been proven to be most effective for improving health outcomes. Physical activity can reduce hemoglobin A_{1C} by 0.4% to 1.0% and improve cardiovascular risk factors (ie, hypertension and dyslipidemia). Randomized clinical trials have reported absolute reductions in microvascular disease (3.5%), such as retinopathy and nephropathy, myocardial infarction (3.3%-6.2%), and mortality (2.7%-4.9%), with intensive glucose-lowering strategies (hemoglobin A_{1C} <7%) vs conventional treatment 2 decades after trial completion. First-line medications for type 2 diabetes include metformin and, in patients with cardiovascular or kidney comorbidities or at high cardiovascular risk, glucagon-like peptide-1 receptor agonists (GLP-1RAs) or sodium-glucose cotransporter 2 inhibitors (SGLT2is). Common add-on medications include dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1RAs, dipeptidyl peptidase-4 inhibitors, sulfonylureas, and thiazolidinediones. Approximately one-third of patients with type 2 diabetes require treatment with insulin during their lifetime. Several randomized clinical trials have demonstrated benefits of specific SGLT2i and GLP-1RA medications compared with placebo for atherosclerotic cardiovascular disease (12%-26% risk reduction), heart failure (18%-25% risk reduction), and kidney disease (24%-39% risk reduction) over 2 to 5 years. Most trial participants with type 2 diabetes were taking metformin. High-potency GLP-1RA and dual GIP/GLP-1RA medications result in weight loss of greater than 5% in most individuals with type 2 diabetes, and weight loss may exceed 10%.

CONCLUSIONS Type 2 diabetes affects up to 14% of the global population and is associated with preventable long-term complications, such as cardiovascular disease, kidney failure, vision loss, and increased mortality. In addition to lifestyle modifications including diet, exercise, and weight management, metformin is generally first-line therapy for attainment of hemoglobin A_{1C} targets. For individuals with type 2 diabetes and cardiovascular or kidney disease or at high cardiovascular risk, guidelines recommend early treatment with SGLT2i and/or GLP-1RA medications.

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Author Affiliations: Division of Endocrinology, Diabetes, and Metabolism, The Johns Hopkins University School of Medicine, Baltimore, Maryland (Kalyani); College of Pharmacy and Pharmaceutical Sciences, Washington State University, Spokane (Neumiller); Division of General Internal Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland (Maruthur); Diabetes Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston (Wexler).

Corresponding Author: Rita R. Kalyani, MD, MHS, Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Johns Hopkins University School of Medicine, 1830 E Monument St, Ste 333, Baltimore, MD 21287 (rrastogi@jhmi.edu).

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The number of people with diabetes worldwide was estimated to be between 589 million and 828 million during 2022 to 2024,[1,2] with type 2 diabetes comprising 90% to 95% of cases.[1,3,4] Insulin resistance may be present for 10 years or longer prior to diagnosis.[5] Although the global prevalence is rising (estimates range from 11%-14% of adult population), the incidence of type 2 diabetes has stabilized or decreased in most places worldwide.[6,7] The prevalence of diabetes in US adults is 15.8%.[4] In individuals with prediabetes, type 2 diabetes can be prevented or delayed with changes in health behaviors that lead to weight loss or pharmacotherapy.[8]

Risk factors for type 2 diabetes include overweight and obesity, physical inactivity, age, family history, race and ethnicity, history of gestational diabetes, and presence of other conditions (eg, hypertension, dyslipidemia, cardiovascular disease).[9-14] More than 600 genetic variants are associated with an increased risk of type 2 diabetes.[15] Although body mass index has a stronger association with type 2 diabetes than genetic risk scores,[16] approximately 10% of individuals with type 2 diabetes do not have overweight or obesity.[3]

Globally, 32.2% of people with type 2 diabetes have cardiovascular disease.[17] In the US, 1 in 10 individuals with diabetes have severe vision loss or blindness.[3] Diabetes is a leading cause of kidney failure, nontraumatic lower extremity amputation, and death (30.4 deaths per 100 000 population).[3,18] Diabetes-related comorbidities also include metabolic dysfunction–associated steatotic liver disease,[19] cancers such as colorectal and breast,[20] and dementia.[21] (eFigure 1 in the Supplement).[20,21]

Although hemoglobin A_{1C} (HbA_{1C}) lowering with medications such as metformin and treatment of cardiovascular risk factors such as hypertension and hyperlipidemia are important,[14] the availability of newer glucose-lowering drugs (glucagon-like peptide-1 receptor agonists [GLP-1RAs] and sodium-glucose cotransporter 2 inhibitor [SGLT2i] medications) that have cardiovascular, kidney, and weight loss benefits has led to changes in diabetes care recommendations. This review summarizes current evidence regarding the diagnosis and treatment of people with type 2 diabetes (**Box 1**).

Box 1. Commonly Asked Questions About Type 2 Diabetes

What tests can be used to diagnose type 2 diabetes?
Any of the following blood tests may be used to diagnose type 2 diabetes: fasting plasma glucose, 2-hour plasma glucose during a 75-g oral glucose tolerance test, or hemoglobin A_{1C} (HbA_{1C}). For routine screening, fasting plasma glucose and HbA_{1C} are typically preferred, although, the 2-hour plasma glucose is a more sensitive test and may help identify individuals who might otherwise not be identified as having diabetes using the other tests (ie, cystic fibrosis-related diabetes or post-transplantation diabetes).

Is metformin still first-line treatment for type 2 diabetes?
Many guidelines continue to recommend metformin as first-line treatment for type 2 diabetes. However, most guidelines now recommend that patients with type 2 diabetes and atherosclerotic cardiovascular disease, heart failure, or kidney disease receive treatment with sodium-glucose cotransporter 2 inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RAs) prior to or concurrently with metformin due to the decreased risk of disease progression with use of these medications.

When should injectable medications for type 2 diabetes be started?
For individuals with hyperglycemia despite use of metformin or other oral glucose-lowering agents, a GLP-1RA or dual glucose-dependent insulinotropic polypeptide/GLP-1RA is initially preferred over insulin per some guidelines for people with type 2 diabetes due to decreased hypoglycemia and increased weight loss. However, patients with severe hyperglycemic symptoms (ie, polyuria or polydipsia), unexpected weight loss, and/or HbA_{1C} >10% usually require treatment with insulin.

Methods

We searched PubMed for English-language articles published within 5 years before and through June 12, 2024, and updated the search for additional articles published through February 14, 2025, using title keywords for diagnosis and treatment of type 2 diabetes (Supplement). We focused on high-quality studies and supplemented our search by identifying additional articles from references of selected articles and reviewed relevant current practice guidelines.

Of 2016 articles identified, 126 were included, consisting of 47 randomized clinical trials, 22 observational studies, 21 systematic reviews and/or meta-analyses, 21 guidelines, 12 narrative reviews, and 3 drug or device reference guides.

Units of Measure

We report laboratory values primarily in conventional units. To convert glucose from mg/dL to mmol/L, multiply values by 0.0555. To convert HbA_{1c} to mmol/mol, use the following equation: $(10.93 \times HbA_{1c}) - 23.50$.

Diagnosis

Diabetes becomes clinically evident when elevated blood glucose levels cause glycosuria with resultant polyuria, polydipsia, fatigue, blurry vision, and unintentional weight loss. However, most individuals with type 2 diabetes are asymptomatic at diagnosis, and routine screening is recommended (**Box 2**).[14,22]

The cut points recommended by the American Diabetes Association and World Health Organization for diagnosis of diabetes in nonpregnant adults are HbA_{1C} greater than or equal to 6.5%, fasting plasma glucose greater than or equal to 126 mg/dL after 8 hours of no caloric intake, 2-hour plasma glucose greater than or equal to 200 mg/dL during 75-g oral glucose tolerance testing, or unequivocal hyperglycemia including classic symptoms of hyperglycemia or life-threatening hyperglycemic crisis (ie, diabetic ketoacidosis or hyperosmolar hyperglycemic state) and random plasma glucose level greater than or equal to 200 mg/dL.[14,23] Diagnosis requires 2 test results above the diagnostic threshold obtained at the same time (eg, HbA_{1C} and fasting plasma glucose) or at 2 different times, which may be either a repeat of the initial test or a different test.

HbA_{1C} is an indirect measure of glucose exposure from nonenzymatic glycation of hemoglobin and represents a weighted mean plasma glucose over the lifespan of the red blood cell, usually 2 to 3 months. HbA_{1C} generally has greater reliability than glucose levels, but may not accurately reflect time-averaged glucose levels in individuals with some hemoglobinopathies, pregnancy, HIV, recent blood transfusion, iron deficiency anemia, hemodialysis, or hemolytic

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anemia.[14,23] For these individuals, plasma glucose criteria are recommended for diagnosis. Recent physical activity, illness, or acute stress can raise or lower fasting glucose levels. The 2-hour plasma glucose level is more sensitive for diagnosis than fasting glucose or HbA_{1C} in identifying individuals with diabetes, and is the preferred test to diagnose cystic fibrosis-related diabetes or posttransplant diabetes; however, it is more cumbersome to perform and has greater day-to-day variability.[14]

Adult-onset type 1 diabetes and other types of diabetes, such as monogenic diabetes syndromes or diabetes secondary to medical conditions such as pancreatitis, may be misdiagnosed as type 2 diabetes, which can potentially delay initiation of appropriate treatment.[24] In adults with suspected type 1 diabetes (eg, body mass index <25, age <35 years, strong personal or family history of autoimmunity), testing with islet autoantibodies (initially glutamic acid decarboxylase and, if results are negative, then islet tyrosine phosphatase 2, zinc transporter 8, and/or insulin autoantibodies) can help identify type 1 diabetes.[14] Clinical history and additional tests can help differentiate type 2 diabetes from other types of diabetes (**Table 1**).

Box 2. Screening for Type 2 Diabetes

US Preventive Services Task Force

The US Preventive Services Task Force recommends screening for type 2 diabetes in adults aged 35 to 70 years who have overweight (body mass index [BMI] ≥25) or obesity (BMI ≥30) and that screening every 3 years may be reasonable for those with normal glucose levels.[22]

American Diabetes Association

The American Diabetes Association recommends that all adults aged ≥35 years should be screened for type 2 diabetes at a minimum every 3 years. Adults of any age who have a history of gestational diabetes or who have overweight or obesity (BMI ≥25 or ≥23 in individuals of Asian ancestry) along with additional risk factors such as family history in a first-degree relative (ie, parent or sibling) are recommended to have screening every 1-3 years depending on risk status. Screening for type 2 diabetes is recommended yearly in individuals with prediabetes, defined by the American Diabetes Association as fasting plasma glucose 100-125 mg/dL, 2-hour plasma glucose during 75-g oral glucose tolerance test of 140-199 mg/dL, or hemoglobin A_{1C} of 5.7% to 6.4%.[14]

Management

Health Behaviors

Weight management, including dietary modifications, is a fundamental component of diabetes treatment. However, no specific diet has been proven most effective for improving HbA_{1C}, weight loss, or health outcomes. In meta-analyses of people with diabetes (type 1 and 2), clinically meaningful HbA_{1C} reductions have been reported for Mediterranean-style vs control diets (difference in HbA_{1C}, −0.39% [95% CI, −0.58% to −0.20%]), the Dietary Approaches to Stop Hypertension vs control diets (difference in HbA_{1C}, −0.53% [95% CI, −0.62% to −0.43%]), and low- vs high-carbohydrate diets (difference in HbA_{1C} at 6 mo, −0.36% [95% CI, −0.62% to −0.09%]).[25-27] In a trial of 7447 participants in Spain at high cardiovascular risk (50% with diabetes), the 5-year absolute risk of the cardiovascular primary end point (myocardial infarction, stroke, or death from cardiovascular causes) was 3.8% (95% CI, 3.2%-4.4%) in the group randomized to receive a Mediterranean diet combined with extra virgin olive oil or nuts vs 5.7% (95% CI, 4.6%-6.9%) in the control group (intention-to-treat hazard ratio, 0.70 [95% CI, 0.55-0.89]).[28]

Medical nutrition therapy is individualized, in-depth nutrition therapy delivered by a registered dietitian. A systematic review of 18 randomized and nonrandomized clinical trials reported that medical nutrition therapy decreased HbA_{1C} among patients with type 2 diabetes by 0.3% to 2% at 6 months.[29,30] Diabetes self-management education and support encompasses coping, diet, physical activity, medications, self-monitoring, complications, and problem-solving in diabetes.[31] A meta-analysis of 20 randomized clinical trials comparing diabetes self-management education and support with usual care reported a pooled HbA_{1C} difference of −0.60% (95% CI, −0.85% to −0.35%).[32] All types of physical activity, including aerobic and resistance, are beneficial for patients with type 2 diabetes.[14] A meta-analysis of 126 randomized clinical trials (6718 patients) reported the optimal dose of physical activity for people with type 2 diabetes was 1100 metabolic-equivalent minutes per week (equivalent to approximately 244 minutes/week of moderate-intensity aerobic physical activity). Dose-associated HbA_{1C} reductions with this level of activity ranged from 0.4% to 1.0%.[33]

For persons with diabetes and overweight or obesity, American Diabetes Association guidelines recommend restriction of energy intake and increased energy expenditure (500-750 kcal/d energy deficit) to promote weight loss.[14] The DiRECT Study, an open-label, cluster-randomized trial of 306 individuals from 49 primary care practices in the UK, reported that a very low–calorie formula diet (825-853 kcal/d) followed by stepped food reintroduction achieved remission of type 2 diabetes (HbA_{1C} <6.5% without diabetes medications for at least 2 months) among 46% of participants in the intervention group vs 4% in the control group at 12 months (odds ratio, 19.7 [95% CI, 7.8-49.8]).[34]

The Action for Health in Diabetes (Look AHEAD) randomized clinical trial (including 5145 overweight persons with type 2 diabetes) reported that a long-term behavioral weight loss intervention including a goal of at least 175 minutes per week of moderate-intensity physical activity, compared with diabetes self-management education and support, resulted in no difference between groups for the primary cardiovascular outcome over a median of 9.6 years of follow-up. However, the weight loss intervention was associated with sustained weight loss, lower HbA_{1C}, delayed progression of kidney disease, and improvements in quality of life, depression, sleep apnea, urinary incontinence, and health care utilization and costs.[35]

Glycemic Targets for Microvascular and Macrovascular Complications

Multiple trials have demonstrated that achieving an HbA_{1C} less than 7% in nonpregnant adults reduces the risk of microvascular complications such as retinopathy, neuropathy, and nephropathy.[14] The UK Prospective Diabetes Study randomly assigned 4209 patients with newly diagnosed type 2 diabetes to receive conventional (primarily diet) vs intensive (insulin, sulfonylurea, or, if overweight, metformin) treatment, with mean attained HbA_{1C} of 7.9% vs 7.0%,

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Table 1. Differentiating Type 2 Diabetes From Other Types of Diabetes in Nonpregnant Adults

Category	Type 2 diabetes	Type 1 diabetes	Monogenic diabetes syndromes (ie, MODY)	Types of diabetes secondary to other medical conditions
Epidemiology[a]	90%-95%	5%-10%	<5%	<5%
Pathophysiology	Nonautoimmune progressive loss of insulin secretion from β cells, usually in the setting of insulin resistance	Autoimmune β-cell destruction, usually leading to absolute or near-absolute insulin deficiency	Rare form of diabetes caused by a variant in a single gene disrupting β-cell glucose sensing or insulin production, inherited in an autosomal dominant manner; the most common forms are GCK-MODY (MODY2; glucose-sensing defect), HNF1A-MODY (MODY3), and HNF4A-MODY (MODY1)	Many different secondary forms of diabetes exist; examples include diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), diabetes due to endocrinopathies such as Cushing syndrome or acromegaly, or diabetes secondary to SARS-CoV-2 infection
Age at diagnosis	Usually ≥35 y but increasingly seen in youth and younger adults, especially in the setting of obesity and/or family history	Can occur in adults at any age, often with more indolent onset compared with children (termed *latent autoimmune diabetes in adults*)	Usually <25 y	Any age
Degree of hyperglycemia on presentation	Usually mild (blood glucose <250 mg/dL) if detected early; however, can be moderate or severe in long-standing undiagnosed diabetes.	Usually moderate (blood glucose of 250-600 mg/dL); can be severe (blood glucose >600 mg/dL) in some cases	Mild; usually HbA_{1C} <7.5% at diagnosis	Mild, moderate, or severe
Symptoms	Can be asymptomatic or with symptoms	Usually with catabolic symptoms (polyuria, polydipsia, weight loss); can be asymptomatic in adults	Usually asymptomatic	Can be asymptomatic or with symptoms
BMI	Usually BMI ≥25	Usually BMI <25, but can be diagnosed in those with overweight or obesity	Variable, but obesity usually not present	Any
Family history	Often a first-degree relative with type 2 diabetes, but not always	Sometimes a first-degree relative with type 1 diabetes or other autoimmune disease; 85% have no family history	Autosomal dominant family history, confirmed to be MODY diabetes	Not usually
Diabetic ketoacidosis	Can be seen on presentation in those with severe insulin deficiency or glucotoxicity (termed *ketosis-prone type 2 diabetes*); euglycemic diabetic ketoacidosis has been described in individuals taking SGLT2is	Ketoacidosis common on presentation in children; variable on presentation in adults	Unlikely	Rare; has been reported with SARS-CoV-2 infection and can occur with severe pancreatitis
Autoantibodies present	Not usually seen, but can be present in up to 10% of individuals, depending on the population	Common, but 5%-10% will not have antibodies present on diagnosis, and levels can wane over time; the following antibodies are often tested: glutamic acid decarboxylase (GAD), islet tyrosine phosphatase-related islet antigen 2 (IA-2), zinc transporter 8 (ZnT8) and/or insulin autoantibodies (IAA)	Unlikely	Unlikely
Race and ethnicity	Any; more common in Asian American and Pacific Islander, Black, Latino, and Native American individuals than White individuals	Any; more common with European ancestry	Any; most described in populations of European ancestry	Any
Genetic testing	Not commercially available	Not commercially available; currently only in research studies	Yes; required for definitive diagnosis	Not commercially available
Duration prior to diagnosis	Long (years)	Short (months)	Long (years; potentially lifelong undiagnosed in mild cases)	Variable
Stimulated C-peptide[b]	Detectable	Low or undetectable (<200 pmol/L); may be detectable soon after diagnosis or for prolonged duration in adult-onset	Detectable	Variable
Drugs that may exacerbate or contribute to development of diabetes	Long-term glucocorticoids, use of immunosuppressant drugs after organ transplant such as tacrolimus and cyclosporine (ie, new-onset diabetes after transplant),[c] and second-generation antipsychotics such as olanzapine and clozapine[d]	Immune checkpoint inhibitors such as nivolumab and pembrolizumab (for cancer)	None	Antiretroviral therapies (ie, certain protease inhibitors and nucleoside reverse transcriptase inhibitors) in people with HIV[d]; glucocorticoid treatment with active COVID-19

(continued)

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Table 1. Differentiating Type 2 Diabetes From Other Types of Diabetes in Nonpregnant Adults (continued)

Category	Type 2 diabetes	Type 1 diabetes	Monogenic diabetes syndromes (ie, MODY)	Types of diabetes secondary to other medical conditions
Related comorbidities	See eFigure 1 in the Supplement	Other autoimmune conditions	Associated features of a specific MODY type (eg, renal cysts, partial lipodystrophy, maternally inherited deafness, severe insulin resistance in the absence of obesity)	Depends on secondary medical condition
Treatment	Lifestyle change, oral agents, noninsulin injectables, insulin	Insulin	Depends on type; no treatment (GCK-MODY), sulfonylureas (HNF1A-MODY or HNF4A-MODY), sometimes insulin is needed	Variable, depends on secondary medical condition; DPP4i or GLP-1 less preferred in patients with pancreatitis

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DPP4i, DPP-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; MODY, maturity-onset diabetes of the young; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

[a] The exact prevalence of different types of diabetes may depend on the population; thus, ranges are provided for each type.

[b] Refer to endocrinologist for testing; usually performed after stimulation with glucagon injection or mixed meal test. A C-peptide measurement (with simultaneous glucose) obtained within 5 hours of eating can replace a formal C-peptide stimulation test for classification.

[c] Screen with oral glucose tolerance test after immunosuppressive regimen is stable.

[d] Screen for prediabetes or diabetes at baseline when prescribed these drugs; repeat at 3 months, if clinically indicated, and annually.[14]

respectively.[36,37] An observational study that published follow-up data (median of 17.5 years [range, 0-42 years]) on 1489 (97.6%) of the 1525 surviving participants reported reductions in all-cause mortality (2.7%-4.9%), myocardial infarction (3.3%-6.2%), and microvascular disease defined as vitreous hemorrhage, retinal photocoagulation, death due to kidney disease, or kidney failure (3.5%) in those previously randomized to receive intensive treatment vs conventional therapy ($P < .05$ for all comparisons).[38]

ACCORD,[39] ADVANCE,[40] and VADT[41] were trials of intensive vs standard glycemic control using oral glucose-lowering agents or insulin (conducted prior to availability of SGLT2is and GLP-1RAs) in participants with longer duration of type 2 diabetes (mean of 10 years); approximately one-third of participants in each trial had cardiovascular disease. ACCORD included 10 251 patients with type 2 diabetes; the intensive vs standard care group achieved mean HbA_{1C} of 6.4% (target <6%) vs 7.5%, respectively, at 1 year. ADVANCE enrolled 11 140 patients with type 2 diabetes and targeted HbA_{1C} less than or equal to 6.5% in the intensive group (mean HbA_{1C} of 6.5% in the intensive group vs 7.3% in the standard care group). VADT enrolled 1791 veterans with type 2 diabetes, targeting a difference in HbA_{1c} of 1.5% between the groups (mean HbA_{1C} of 6.9% in the intensive group vs 8.4% in the standard care group). Intensive control reduced retinopathy progression in ACCORD (7.3% vs 10.4%; $P = .003$)[42] and incidence of nephropathy in ADVANCE (4.1% vs 5.2%; $P = .006$).[40] However, the only microvascular complication that showed a significant reduction among patients treated with intensive glycemic control in VADT was a decrease in worsening albuminuria.[41]

Although these studies demonstrate that more intensive glycemic targets (HbA_{1C} <6.5%) may benefit microvascular disease, these targets do not have consistent benefits for macrovascular disease, defined as nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. In ACCORD, compared with the standard care group, the intensive glycemic control group had increased hypoglycemia (10.5% vs 3.5%; $P < .001$), weight gain greater than 10% (28% vs 14%; $P < .001$), and mortality (5% vs 4%; hazard ratio, 1.22 [95% CI, 1.01-1.46]), prompting early trial discontinuation.[39,43] ADVANCE and VADT reported no significant differences between intensive glycemic control vs standard care on macrovascular outcomes during the trial periods.[40,41] An observational study with 10-year follow-up of VADT participants reported an absolute risk reduction of 8.6 major cardiovascular events per 1000 person-years, although this benefit was no longer present at 15 years.[44]

In a meta-analysis and systematic review of 15 randomized clinical trials and observational studies (783 255 patients) comparing intensive control (HbA_{1C} <7.5%) vs standard care in adults 60 years or older or frail adults of any age with type 2 diabetes, there was no difference in mortality, but intensive control was associated with both a reduction in microvascular and macrovascular complications and increased risk for severe hypoglycemia.[45] Older adults with cognitive or functional limitations and those with reduced life expectancy experience less benefit from intensive glycemic targets and more harm from overtreatment, including increased risk of severe hypoglycemia, which may lead to falls and fractures.[46]

Glucose Monitoring

In addition to HbA_{1C} testing, ambulatory glucose monitoring with fingerstick blood glucose monitoring (BGM) and/or continuous

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glucose monitoring (CGM) is important for achieving glycemic goals in many individuals with type 2 diabetes. Although BGM has not been demonstrated to decrease HbA_{1C} in type 2 diabetes not treated with insulin,[47] it can be considered to help some patients adjust lifestyle or medication regimens.[14] (eFigure 2 in the Supplement). For patients only taking basal insulin, once-daily fasting BGM can suffice to achieve fasting glucose targets (80-130 mg/dL for many nonpregnant adults based on American Diabetes Association guidelines) and reduce HbA_{1C}.[14,48]

A systematic review and meta-analysis of CGM use in adults with type 2 diabetes (12 randomized clinical trials with 1248 participants taking insulin, GLP-1RA, or oral glucose-lowering medications) reported that CGM led to a mean difference in HbA_{1C} reduction over 10 to 34 weeks of −0.31% (95% CI, −0.43% to −0.19%) compared with BGM.[49] In a randomized clinical trial of 224 participants with type 2 diabetes taking insulin, CGM decreased hypoglycemic episodes, reducing time with blood glucose less than 70 mg/dL by 0.47 hours per day compared with BGM.[50] CGM accuracy is slightly lower the first day following sensor insertion and when glucose levels are rapidly changing.[51]

For people taking multiple daily injections of insulin, evidence-based guidelines recommend BGM be performed at a minimum prior to meals and at bedtime to guide insulin dosing and avoid hypoglycemia, and that CGM be offered to all people with type 2 diabetes taking insulin and considered for those taking other noninsulin glucose-lowering therapies, with a goal of achieving greater than 70% of time in range (blood glucose of 70-180 mg/dL) for most nonpregnant adults.[14,52,53]

Glucose-Lowering Medications for Type 2 Diabetes

The number of glucose-lowering medications for treatment of type 2 diabetes has increased over recent years with currently available therapies targeting different organs and sites of action that contribute to the development of hyperglycemia (**Figure**).[54]

Initiation of glucose-lowering pharmacotherapy is associated with reduced long-term microvascular and macrovascular complications.[36,37,55-83] Patients presenting with severe hyperglycemia symptoms such as polyuria and polydipsia, unexpected weight loss, or HbA_{1C} greater than 10% should initially be treated with insulin. In asymptomatic patients diagnosed with type 2 diabetes, most guidelines recommend metformin as the first medication in those without cardiovascular comorbidities (ie, atherosclerotic cardiovascular disease or heart failure) or chronic kidney disease. This recommendation is based on the high glycemic efficacy, low hypoglycemia risk, general tolerability, and low cost of metformin.[84] The major barrier to use of metformin is gastrointestinal adverse effects such as diarrhea (**Table 2**), which may be ameliorated by slow dose titration (eg, starting with 500 mg once daily followed by gradual dose escalation by 500 mg every week until target dose is reached)[89] or switching to an extended-release formulation. A meta-analysis of 15 randomized clinical trials (N = 3765) reported that extended-release metformin was associated with a nonsignificant reduction in gastrointestinal adverse effects compared with immediate-release metformin (24.6% vs 28.1%; odds ratio, 0.76 [95% CI, 0.58-1.00]).[90]

A randomized trial of 5047 patients with type 2 diabetes who were taking metformin assigned patients to receive a sulfonylurea (glimepiride), DPP-4 inhibitor (sitagliptin), GLP-1 receptor agonist (liraglutide), or basal insulin glargine. At 5 years of follow-up, the incidence of HbA_{1C} greater than 7.0% was lower with the addition of insulin glargine or liraglutide (26.5 and 26.1 per 100 participant-years, respectively) than glimepiride or sitagliptin (30.4 and 38.1 per 100 participant-years, respectively) ($P < .001$ for a global test of differences across all groups).[91] Patients in the GLP-1RA group had more weight loss (mean, −3.5 kg). For individuals taking 1 or more oral glucose-lowering drugs at maximally tolerated doses who require injectable therapies to meet glycemic targets (ie, HbA_{1C} level more than 1.5%-2% above goal) in the absence of severe hyperglycemia symptoms, use of a GLP-1RA or dual GLP-1/GIP-RA is initially preferred to insulin due to decreased hypoglycemia and increased weight loss by many guidelines (**Table 3** and **Table 4**).[14] Newer, high-potency weekly GLP-1RAs (ie, high-dose semaglutide or dulaglutide) and dual GIP/GLP-1RAs (ie, tirzepatide) are associated with mean HbA_{1C} reductions up to approximately 2% to 2.5% and weight reductions of greater than 5% from baseline in most individuals, with some exceeding 10%.[80]

Insulin therapy is eventually required by up to one-third of adults with type 2 diabetes to maintain glycemic goals as β-cell function declines.[14,103] A variety of insulin formulations with different onsets of action and durations of effect are available (Table 3; eFigure 3 in the Supplement).[92] Basal insulin is the most common initially prescribed insulin in type 2 diabetes, with addition of insulin at meals as needed to target postprandial hyperglycemia (ie, 1-2 hours after the beginning of the meal) and achieve glycemic targets.[14] Mixed insulin regimens can be administered individually (eg, separate basal and prandial injections) or as premixed (eg, 70/30) preparations, depending on patient preferences for injection frequency and need for dosing flexibility.[92] For individuals requiring large doses of insulin due to high levels of insulin resistance, concentrated insulin products (ie, 2-5 times more insulin per unit volume) can reduce injection volume and discomfort (Table 3).

Insulin pumps are palm-sized devices that deliver rapid-acting insulin (ie, aspart or lispro) throughout the day through tubing and a cannula inserted under the skin or attached directly to the skin. In a randomized multicenter clinical trial of 319 patients over 13 weeks, use of an automated insulin pump paired with CGM and an algorithm to automatically adjust insulin delivery based on real-time glucose levels led to a mean HbA_{1C} reduction of −0.6% (95% CI, −0.8% to −0.4%; $P < .001$) compared with multiple daily injections of insulin and CGM alone.[104] Evidence-based guidelines recommend insulin pump therapy be offered to individuals with type 2 diabetes taking multiple daily injections of insulin who are capable of using these devices safely.[14,52,53]

Comorbidity Considerations When Selecting Glucose-Lowering Medications

For people with type 2 diabetes who have established or are at high risk for atherosclerotic cardiovascular disease, heart failure (HF), or chronic kidney disease (CKD), evidence-based guidelines recommend SGLT2is or GLP-1RAs oftentimes irrespective of HbA_{1C} levels (Table 4).[105]

Atherosclerotic Cardiovascular Disease

Specific SGLT2i[61,62] and GLP-1RA[70-72] medications have demonstrated significant risk reductions for major adverse cardiovascular events in large trials that mostly enrolled participants with type 2

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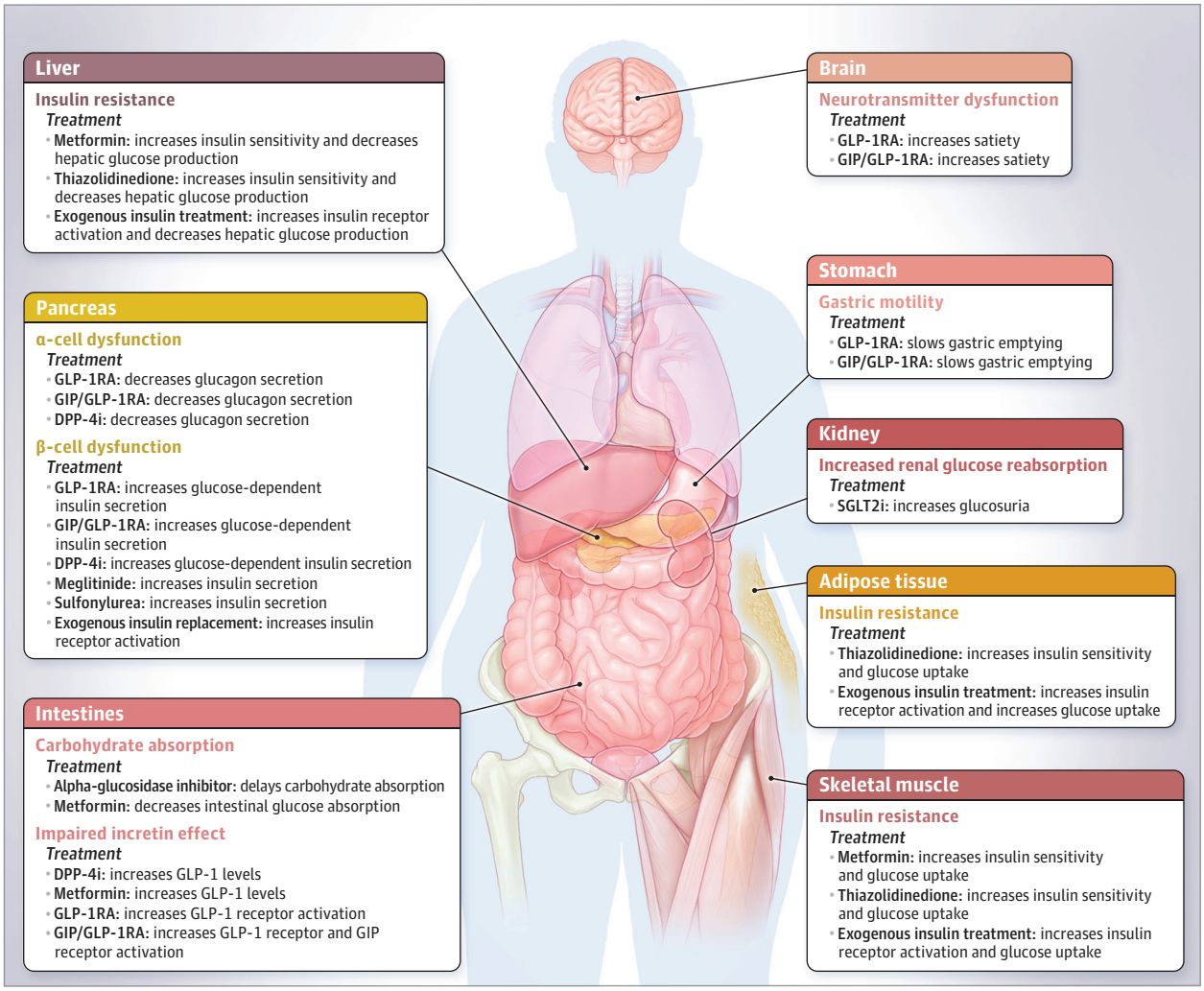
Figure. Key Pathophysiologic Defects in Type 2 Diabetes and Primary Sites of Action of Glucose-Lowering Medications


Liver
Insulin resistance
Treatment
• Metformin: increases insulin sensitivity and decreases hepatic glucose production
• Thiazolidinedione: increases insulin sensitivity and decreases hepatic glucose production
• Exogenous insulin treatment: increases insulin receptor activation and decreases hepatic glucose production
Pancreas
α-cell dysfunction
Treatment
• GLP-1RA: decreases glucagon secretion
• GIP/GLP-1RA: decreases glucagon secretion
• DPP-4i: decreases glucagon secretion
β-cell dysfunction
Treatment
• GLP-1RA: increases glucose-dependent insulin secretion
• GIP/GLP-1RA: increases glucose-dependent insulin secretion
• DPP-4i: increases glucose-dependent insulin secretion
• Meglitinide: increases insulin secretion
• Sulfonylurea: increases insulin secretion
• Exogenous insulin replacement: increases insulin receptor activation
Intestines
Carbohydrate absorption
Treatment
• Alpha-glucosidase inhibitor: delays carbohydrate absorption
• Metformin: decreases intestinal glucose absorption
Impaired incretin effect
Treatment
• DPP-4i: increases GLP-1 levels
• Metformin: increases GLP-1 levels
• GLP-1RA: increases GLP-1 receptor activation
• GIP/GLP-1RA: increases GLP-1 receptor and GIP receptor activation
Brain
Neurotransmitter dysfunction
Treatment
• GLP-1RA: increases satiety
• GIP/GLP-1RA: increases satiety
Stomach
Gastric motility
Treatment
• GLP-1RA: slows gastric emptying
• GIP/GLP-1RA: slows gastric emptying
Kidney
Increased renal glucose reabsorption
Treatment
• SGLT2i: increases glucosuria
Adipose tissue
Insulin resistance
Treatment
• Thiazolidinedione: increases insulin sensitivity and glucose uptake
• Exogenous insulin treatment: increases insulin receptor activation and increases glucose uptake
Skeletal muscle
Insulin resistance
Treatment
• Metformin: increases insulin sensitivity and glucose uptake
• Thiazolidinedione: increases insulin sensitivity and glucose uptake
• Exogenous insulin treatment: increases insulin receptor activation and glucose uptake

There are multiple pathophysiological defects in various organs that contribute to the development of hyperglycemia in type 2 diabetes.[54] Different classes of glucose-lowering medications are currently available, each with specific mechanisms of action to lower blood glucose that target these defects. Commonly used medication for type 2 diabetes are included. DPP-4i indicates dipeptidyl peptidase-4 inhibitor; GIP/GLP-1RA, glucose-dependent insulinotropic polypeptide/ glucagon-like peptide-1 receptor agonist; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

diabetes and history of established cardiovascular diseases; more than 70% of participants were receiving background metformin therapy.[106] Trials with agents from the DPP-4 inhibitor class have generally established safety, but not cardiovascular benefit.[14]

A meta-analysis of 6 trials of 4 SGLT2 inhibitors, including 46 969 participants with type 2 diabetes (66% with established cardiovascular disease) with median follow-up from 2.4 to 4.2 years reported reduction in risk of the primary 3-point major adverse cardiovascular events outcome of myocardial infarction, stroke, or cardiovascular death (hazard ratio, 0.90 [95% CI, 0.85-0.95]). Significant reductions were also observed in secondary outcomes including cardiovascular death, hospitalization for heart failure, and kidney disease progression, defined as worsening estimated glomerular filtration rate (eGFR) or creatinine, kidney failure, death from renal causes, or cardiovascular death.[107]

Similarly, a meta-analysis of 7 trials of 6 injectable GLP-1RAs and 1 oral GLP-1RA among 56 004 participants with type 2 diabetes (76% with established cardiovascular disease) over a median follow-up of 1.3 to 5.4 years reported a reduction in both the primary major adverse cardiovascular events outcome (10.5% with GLP-1RA treatment vs 11.8% with placebo; hazard ratio, 0.88 [95% CI, 0.82-0.94]) and secondary outcomes including a reduction in cardiovascular mortality (fatal or nonfatal stroke and fatal or nonfatal myocardial infarction).[108]

Cardiovascular effects of glucose-lowering medications approved by the US Food and Drug Administration prior to 2008 have a weaker evidence base because large, randomized cardiovascular outcome trials were not mandated at the time; however, metformin and pioglitazone likely have cardiovascular benefit.[60,104,105]

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Table 2. Factors for Individualized Selection of Noninsulin Glucose-Lowering Medications in People With Type 2 Diabetes[a]

Drug (glucose-lowering dose)	Glucose-lowering efficacy[55,56,b]	Impact on weight[56,57,c]	Hypoglycemia risk as monotherapy	Impact on comorbidities[d]	Cost[58,f]	Common adverse effects[59,g,e]	Practical considerations[59]
Alpha-glucosidase inhibitors: Acarbose (25-100 mg orally at each meal) Miglitol (25-100 mg orally at each meal)	Intermediate (0.5%)	Neutral	No	Atherosclerotic cardiovascular disease: neutral[8] HF[5]: neutral[85]	$-$$$	Most common adverse effects: abdominal pain (12%-19%), diarrhea (29%-31%), elevated transaminases (14% [acarbose]), flatulence (42%-74%) Contraindications :cirrhosis, inflammatory bowel disease, colonic ulceration, intestinal obstruction, hypersensitivity Warnings/precautions: hypoglycemia (add-on to sulfonylurea and/or insulin); use oral glucose (not sucrose) to treat hypoglycemia	When to use Add-on treatment in individuals who require intermediate levels of HbA_{1C} lowering (0.5%-1% above target); not as commonly used due to gastrointestinal adverse effects Can reduce postprandial hyperglycemia Dosing considerations: Take only when eating Start low dose, titrate slowly to minimize gastrointestinal adverse effects
Biguanides: Metformin (500-2000 mg orally daily)	High (1.0%-2.0%)	Neutral (potential for modest weight loss)	No	Atherosclerotic cardiovascular disease: likely long-term benefit[38,60] Chronic kidney disease: neutral HF: neutral	$	Most common adverse effects[h]: diarrhea (10%-53%), nausea/vomiting (7%-26%), abdominal discomfort (1%-6%) Contraindications: estimated glomerular filtration rate <30 mL/min/1.73 m^2, acute or chronic metabolic acidosis, hypersensitivity Warnings/precautions: vitamin B12 deficiency, lactic acidosis	When to use First-line treatment when initial HbA_{1C} <9%-10% and in absence of life-threatening hyperglycemic crisis (ie, diabetic ketoacidosis or hyperosmolar hyperglycemic state) Can be used at reduced doses (ie, 1000 mg) with estimated glomerular filtration rate 30-45 mL/min/1.73m^2 If gastrointestinal symptoms develop Hold or reduce dose to assess the relationship of symptoms to metformin Consider switching to extended-release formulation Take with food to improve tolerability and/or continue at reduced dose When to hold Prior to procedure with nothing per mouth or illness Day of procedure Resume when eating normally
Dipeptidyl peptidase-4 inhibitors: Alogliptin (6.25-25 mg orally daily) Linagliptin (5 mg orally daily) Saxagliptin (2.5-5 mg orally daily) Sitagliptin (25-100 mg orally daily)	Intermediate (<0.5%)	Neutral	No	Atherosclerotic cardiovascular disease: neutral Chronic kidney disease: neutral HF: potential risk with saxagliptin[77]	$$-$$$	Most common adverse effects: upper respiratory infection (4%-8%), nasopharyngitis (5%-7%), headache (4%-7%) Contraindications: hypersensitivity Warnings/precautions: pancreatitis, hypersensitivity reactions, arthralgia, bullous pemphigoid	When to use Add-on treatment in individuals who require intermediate levels of HbA_{1C} lowering (0.5%-1% above target) without risk of hypoglycemia For patients who desire to maintain weight Combination therapy: Dipeptidyl peptidase-4 inhibitors should not be combined with GLP-1RAs or dual GLP-1/GIP RAs because they act on the same pathway

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Table 2. Factors for Individualized Selection of Noninsulin Glucose-Lowering Medications in People With Type 2 Diabetes[a] (continued)

Drug (glucose-lowering dose)	Glucose-lowering efficacy[55,56,b]	Impact on weight[56,57,c]	Hypoglycemia risk as monotherapy	Impact on comorbidities[d]	Cost[58,f]	Common adverse effects[59,g,e]	Practical considerations[59]
GIP/GLP-1RA: Tirzepatide (2.5-15 mg subcutaneously once weekly)	High (1.0%-2.0%) to very high (2.0%-2.5%)	Loss (high)	No	Atherosclerotic cardiovascular disease: safe[i] Chronic kidney disease: safe[i] HF: benefit in obesity-related HFpEF[109]	$$$$	Most common adverse effects: nausea (18%), diarrhea (17%), vomiting (9%), constipation (7%), dyspepsia (5%), abdominal pain (5%) Contraindications: personal or family history of medullary thyroid cancer or in patients with multiple endocrine neoplasia 2 Warnings/precautions: pancreatitis, hypoglycemia (add-on to sulfonylurea and/or insulin), diabetic retinopathy complications, acute kidney injury, hypersensitivity reactions, acute gallbladder disease	When to use Add-on treatment in individuals taking ≥1 oral glucose-lowering drugs at maximally tolerated doses who require high to very high levels of HbA_{1C} lowering (ie, HbA_{1C} >1.0%-2.5% above goal) Can be used for patients who desire substantial weight loss When to hold Prior to procedures, consider dietary adjustments (eg, liquid diet) or holding therapy (eg, day of procedure for daily formulations or 1 week prior for weekly formulations) in those at high risk for delayed gastric emptying When adding to insulin Reduce then stop prandial insulin Reduce the basal insulin dose as GLP-1 dose increases, guided by glucose monitoring
GLP-1RAs: Dulaglutide (0.75-4.5 subcutaneously once weekly) Exenatide extended release (2 mg subcutaneously once weekly) Liraglutide (0.6-1.8 mg subcutaneously daily) Semaglutide (0.25-2 mg subcutaneously once weekly or 3-14 mg orally daily or 1.5 - 9 mg orally daily)	High (1.0%-2.0%) to very high (2.0%-2.5%)	Loss (intermediate to high)	No	Atherosclerotic cardiovascular disease: benefit on major cardiovascular events with dulaglutide,[70] liraglutide,[71] and semaglutide[72,86] Chronic kidney disease: benefit on progression with semaglutide (subcutaneous)[73] HF: evidence of benefit in obesity-related HFpEF with semaglutide (subcutaneous)[74,75]	$$$$	Most common adverse effects[j]: nausea (8%-21%), vomiting (3%-13%), diarrhea (9%-13%), abdominal pain (6%-11%), constipation (2%-5%) Contraindications: personal or family history of medullary thyroid cancer or in patients with multiple endocrine neoplasia 2 Warnings/precautions; pancreatitis, hypoglycemia (add-on to sulfonylurea and/or insulin), diabetic retinopathy complications, acute kidney injury, hypersensitivity reactions, acute gallbladder disease	When to use First-line treatment in atherosclerotic cardiovascular disease, chronic kidney disease, obesity-related HFpEF Add-on treatment in individuals without cardiovascular or kidney comorbidities taking 1 or more oral glucose-lowering drugs at maximally tolerated doses who require high to very high levels of HbA_{1C} lowering (ie, HbA_{1C} level >1.0%-2.5% above goal) Can be used for patients who desire moderate weight loss When to hold: Prior to procedures, consider dietary adjustments (eg, liquid diet) or holding therapy (eg, day of procedure for daily formulations or 1 week prior for weekly formulations) in those at high risk for delayed gastric emptying Switching GLP-1 formulations: Although there is no standard dose equivalence, the following may be used as a guide: semaglutide oral 14 mg ~ semaglutide subcutaneous 0.5 mg ~ dulaglutide 1.5 mg ~ liraglutide 1.8 mg ~ tirzepatide 2.5 mg[76,80] When adding to insulin: Reduce, then stop prandial insulin Reduce the basal insulin dose as GLP-1 dose increases, guided by glucose monitoring

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Table 2. Factors for Individualized Selection of Noninsulin Glucose-Lowering Medications in People With Type 2 Diabetes[a] (continued)

Drug (glucose-lowering dose)	Glucose-lowering efficacy[55,56,b]	Impact on weight[56,57,c]	Hypoglycemia risk as monotherapy	Impact on comorbidities[d]	Cost[58,f]	Common adverse effects[59,g,e]	Practical considerations[59]
Meglitinides: Nateglinide (60-120 mg orally at each meal) Repaglinide (0.5-2mg orally at each meal)	High (1%-2%)	Gain	Yes	Atherosclerotic cardiovascular disease: neutral[87] HF: neutral[87]	$	Most common adverse effects: hypoglycemia (up to 31%), upper respiratory infection (11%-16%), back pain (4%-5%), flu-like symptoms (4% [nateglinide]), arthropathy (3%-6%), diarrhea (3%-5%) Contraindications: hypersensitivity Warnings/precautions: hypoglycemia risk	When to use Add-on treatment in individuals who require high levels of HbA_{1C} lowering (1%-2% above target); not as commonly used due to multiple daily dosing and risk of hypoglycemia Can reduce postprandial hyperglycemia When to hold Hold day of procedure; resume when eating normally
SGLT2 inhibitors[k]: Bexagliflozin (20 mg orally daily) Canagliflozin (100-300 mg orally daily) Dapagliflozin (5-10 mg orally daily) Empagliflozin (10-25 mg orally daily) Ertugliflozin (5-15 mg orally daily)	Intermediate (0.5%)	Loss (intermediate)	No	Atherosclerotic cardiovascular disease: benefit on major cardiovascular events with canagliflozin[61] and empagliflozin[62] Chronic kidney disease: benefit on progression with canagliflozin,[63] dapagliflozin,[64] and empagliflozin[65] HF: benefit in HFpEF and HFrEF with dapagliflozin [66,69,88] and empagliflozin [67,68]	$-$$$	Most common adverse effects: genital mycotic infections (6%-12%), urinary tract infection (4%-8%), increased urination (2%-7%) Contraindications: hypersensitivity Warnings/precaution: euglycemic diabetic ketoacidosis, volume depletion, severe urinary tract infections, hypoglycemia (add-on to sulfonylurea and/or insulin), Fournier gangrene; lower limb amputation, fractures with canagliflozin	When to use First-line treatment in atherosclerotic cardiovascular disease, chronic kidney disease, HF Add-on treatment in individuals without cardiovascular or kidney comorbidities who require intermediate levels of HbA_{1C} lowering (0.5%-1% above target) Can be used for patients who desire moderate weight loss When to hold Hold 3-4 d prior to procedures Consider holding if risk of dehydration (eg, religious fasting, strenuous exercise on hot day)
Sulfonylureas: Glimepiride (1-8 mg orally daily) Glipizide (IR: 2.5-40 mg orally daily; extended release: 2.5-20 mg orally daily) Glyburide (1.25-20 mg orally daily)	High (1%-2%)	Gain	Yes	Atherosclerotic cardiovascular disease: neutral Chronic kidney disease: neutral HF: neutral	$	Most common adverse effects (glimepiride)[e]: hypoglycemia (20%), headache (8%), nausea (5%), dizziness (5%) Contraindication: hypersensitivity Warnings/precautions: severe hypoglycemia risk, hemolytic anemia (glucose-6-phosphate dehydrogenase deficiency), special warning for increased risk of cardiovascular mortality based on studies with an older-generation sulfonylurea (tolbutamide); glimepiride demonstrated safety[81]	When to use Add-on treatment in individuals who require high levels of HbA_{1C} lowering (1%-2% above target) Inexpensive and can be used when cost is a concern When to hold Day of procedure; resume when eating normally To minimize hypoglycemia In those at higher risk (eg, older adults, chronic kidney disease), do not use glyburide, which is longer-acting and associated with higher risk of hypoglycemia vs other sulfonylureas Glimepiride or glipizide are shorter-acting and preferred Dose cautiously; do not overtreat

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Table 2. Factors for Individualized Selection of Noninsulin Glucose-Lowering Medications in People With Type 2 Diabetes[a] (continued)

Drug (glucose-lowering dose)	Glucose-lowering efficacy[55,56,b]	Impact on weight[56,57,c]	Hypoglycemia risk as monotherapy	Impact on comorbidities[d]	Cost[58,f]	Common adverse effects[59,g,e]	Practical considerations[59]
Thiazolidine-dione: Pioglitazone (15-45 mg orally daily)	High (1%-2%)	Gain	No	Atherosclerotic cardiovascular disease: likely benefit[78,79] Chronic kidney disease: neutral HF: increased risk	$	Most common adverse effects: upper respiratory infection (13%), headache (9%), sinusitis (6%), myalgia (5%), pharyngitis (5%) Contraindications: New York Heart Association class III or IV HF, hypersensitivity Warnings/precautions: HF, liver toxicity, bladder cancer, fluid retention/edema, fractures, macular edema	When to use Add-on treatment in individuals who require high levels of HbA_{1C} lowering (1%-2% above target) Inexpensive, can be used when cost is a concern Dosing considerations[82] Benefits maximized and adverse effects minimized at doses of 15 or 30 mg Weight gain, edema, and heart failure risk higher at 45-mg dose Fracture risk similar across all doses

Abbreviations: GIP, glucose-dependent insulinotropic polypeptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SGLT, sodium-glucose cotransporter.

[a] Commonly used classes of medications currently approved in the US for treatment of type 2 diabetes.

[b] Based on mean hemoglobin A_{1c} (HbA_{1C}) reductions from baseline in clinical trials of drug-naive patients with type 2 diabetes. Individualized glycemic responses vary based on starting HbA_{1C} and other patient factors.

[c] Relative weight loss effect: modest, <5% loss from baseline; intermediate, 5%-10%; high, >10%.

[d] Specific agents have evidence of benefit from dedicated outcome trials.

[e] Rates listed are taken from the glimepiride package insert. Specific rates not provided for glyburide and glipizide.

[f] From National Average Drug Acquisition Cost data. Based on the price of a 30-day supply at the maximum recommended dose. $ = $1-100/mo; $$ = $101-300/mo; $$$ = $301-600/mo; $$$$ = >$600/mo.

[g] Derived from product package insert; ranges for frequency of common adverse effects at highest indicated dose are provided by class unless otherwise indicated. Refer to product-specific labeling for specific rates.

[h] Gastrointestinal adverse event rates across the range of doses for metformin include immediate release and extended-release products; extended-release products are associated with lower rates of diarrhea, nausea, and vomiting. Consider periodic screening for B12 deficiency.[14]

[i] Cardiovascular and kidney outcome trials are ongoing.

[j] Gastrointestinal adverse event rates are for doses approved by the US Food and Drug Administration for glucose lowering. Higher doses for weight loss are associated with higher rates of nausea and vomiting.

[k] Sotagliflozin is a SGLT1/2 inhibitor indicated to reduce the risk of cardiovascular death, hospitalization for HF, and urgent HF visits in adults with HF or type 2 diabetes, CKD, and other cardiovascular risk factors; it is not currently indicated for glucose lowering in type 2 diabetes and thus not included.[83]

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Table 3. Factors for Individualized Selection of Insulin Therapy in People With Type 2 Diabetes[a]

Drug class and agents[b]	Usual dosing range for glucose-lowering[59]	Glucose-lowering efficacy	Cost[58,c]	Safety/tolerability[59,d]	Considerations for dosing and titration [14,92]	Practical considerations
Basal insulin: Human NPH Degludec Glargine Glargine biosimilar (glargine-yfgn, glargine-aglr) and follow-on products[b] Bolus insulin: Human regular Aspart Aspart biosimilar (aspart-szjj)[b] Fast-acting aspart Lispro Lispro biosimilar (lispro-aabc) and follow-on products[b] Glulisine Inhaled insulin Premixed insulin: Aspart 70/30 Lispro 75/25 Lispro 50/50 NPH/regular 70/30 Fixed dose combinations: Degludec/liraglutide Glargine/lixisenatide	Typically up to 200-300 units; above this, consider concentrated insulins[a]	In theory, no limit to HbA_{1C} lowering potential	$ - $$$ Human insulin (NPH, regular) is lower cost than analog insulins; follow-on and biosimilar insulins often lower cost than the reference insulin product	Most common adverse effects Hypoglycemia Injection site reactions Lipohypertrophy or lipoatrophy Weight gain Contraindications: Hypersensitivity Warnings/precautions Never share insulin delivery devices between patients, even if the needle is changed Increased risk of fluid retention/edema; risk increased further when used in combination with thiazolidinediones	Adding basal insulin: Start 10 units or 0.1-0.2 units/kg/d Increase 2 units every 3 d until at FPG target without overnight or midday hypoglycemia If not already on GLP-1RA or dual GLP-1/GIP RA, consider adding Adding prandial insulin: Start with 4 units (or 10% of basal dose) to the largest meal of the day, titrate based on response, then add additional injections in step-wise manner to second and third meals Titrate by 1-2 units (10%-15%) twice weekly Consider premixed insulin in people with meal patterns that match premixed insulin kinetics (eg, large breakfast and supper, small mid-day meal) Switching insulin formulations: If close to glycemic target: Sum the total daily dose of insulin and reduce by 10%, then titrate based on glucose monitoring If well above glycemic target, switch to the equivalent dose, then titrate Anticipate total daily insulin dose reduction with treatment of glucose toxicity and resolution of insulin resistance as counter-regulatory hormone levels and volume depletion resolve	When to use First-line treatment with severe hyperglycemic symptoms (ie, polyuria or polydipsia) and life-threatening hyperglycemic crisis (ie, diabetic ketoacidosis or hyperosmolar hyperglycemic state) and/or HbA_{1C} >10% Add-on treatment for individuals taking 1 or more oral glucose-lowering drugs at maximally tolerated doses who require injectable therapies to meet glycemic targets (ie, HbA_{1C} level more than 1.5%-2% above goal) Basal insulin can be used to target elevated fasting glucose levels (ie, >80-130 mg/dl) Prandial insulin can be used to target elevated postprandial glucose levels within 1-2 h after meal (ie, >180 mg/dl) Impact on key comorbidities: Neutral cardiovascular[93] and kidney effects Hypoglycemia: Analog insulins generally have less hypoglycemia than human insulins When to hold: If nothing per mouth, hold or reduce insulin by 50%-80% to weight- based basal requirement (eg, 0.2-0.3 units/kg ideal body weight)

Abbreviations: FPG, fasting plasma glucose; GIP, glucose-dependent insulinotropic polypeptide; GLP-1RA, glucagon-like peptide-1 receptor agonist; kg, kilograms; NPH, neutral protamine Hagedorn; NPO, nothing per mouth.

[a] Most insulins available on the market are U-100 concentration (U-100 = 100 units of insulin/mL solution). Concentrated insulins include U-200 insulin degludec or U-200 insulin lispro (U-200 = 200 units of insulin/mL solution), U-300 insulin glargine (U-300 = 300 units of insulin/mL solution), and U-500 regular insulin (U-500 = 500 units of insulin/mL solution). Concentrated insulins can be used to reduce injection volume in individuals on high insulin doses.

[b] "Follow-on insulins" broadly refers to copies of an original insulin; "biosimilar insulin" is a specific type of follow-on insulin that has undergone rigorous testing to demonstrate it is highly similar to the reference insulin with no clinically meaningful differences in safety and effectiveness.

[c] Cost information is derived from National Average Drug Acquisition Cost (NADAC) data. Cost ratings are based on the price of a 30-day (1-month) supply at the maximum recommended dose. $ = $1-100/mo; $$ = $101-300/mo; $$$ = $301-600/mo; $$$$ = >$600/mo.

[d] Derived from product package insert information.

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Table 4. Current Clinical Practice Recommendations for Management of Type 2 Diabetes From Major Professional Societies[a]

Category	American Diabetes Association (2025)[14]	American Association of Clinical Endocrinology (2023)[94]	Endocrine Society (older adults, 2019)[95]	American College of Physicians (2024)[96,97]	VA/DoD (US Department of Veterans Affairs /Department of Defense) (2023)[98]	Diabetes Canada (2024)[99]	National Institute for Health and Care Excellence (UK) (2022)[100]	World Health Organization (2018)[101]	International Diabetes Federation (2025)[102]
HbA_{1C} or glucose target for nonpregnant adults (general population)	<7%, individualize <6.5% younger, short duration, if achieved safely <8% older, multiple comorbidities	≤6.5% or as close to normal as is safe and achievable for patients 7%-8% if high risk for hypoglycemia or limited life expectancy	<7.5 to <8.5% depending on health status; minimize hypoglycemia	7%-8%, deintensify if <6.5%	7%-8.5%, individualize	≤6.5% for adults if low risk of hypoglycemia ≤7.0% most adults 7.1%-8.0% Functionally dependent 7.1%-8.5% Recurrent severe hypoglycemia Hypoglycemia unawareness Limited life expectancy Frail elderly and/or dementia	<7% on medication, individualize, maintain lower target if achieved without hypoglycemia	<7% when available, otherwise fasting blood glucose <126 mg/dL (individualize)	General target <7.0% Personalize HbA_{1C} target: higher in older adults and lower in those newly diagnosed If HbA_{1C} assay not available, use any available glucose measure
Healthy lifestyle behaviors	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended	Recommended
First-line medication	Metformin or other agents and combination therapies that provide adequate efficacy to attain HbA_{1C} goals. Use SGLT2i or GLP-1RA with cardiovascular or kidney benefit in the presence of those comorbidities[b]	Metformin in absence of cardiovascular or kidney comorbidities[b] Use SGLT2i or GLP-1RA with cardiovascular or kidney benefit in the presence of those comorbidities[b]	Metformin if tolerated in older adults	Metformin	Based on cardiovascular and kidney comorbidities, efficacy and risk-benefit ratio of each medication class	Metformin	Metformin	Metformin	Metformin In obese persons, consider metformin and GLP-1 RA (optimal care) or metformin and SGLT2i (basic care; SGLT2i available in many low- and middle-income countries at affordable cost)
Cardiovascular and kidney protective SGLT2i or GLP-1RA in those with ASCVD or high-risk ASCVD[c]	Recommended Independent of HbA_{1C}	Recommended Independent of HbA_{1C}		Recommended And, add as next step after metformin for inadequate glycemic control (regardless of comorbidities)	Recommended Independent of HbA_{1C}	Recommended Independent of HbA_{1C}	Recommended ASCVD: SGLT2i High risk for ASCVD: consider SGLT2i		Recommended GLP-1 RA or SGLT2i (optimal care) SGLT2i (basic care) And, add as next step after metformin for inadequate glycemic control (regardless of comorbidities)

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Table 4. Current Clinical Practice Recommendations for Management of Type 2 Diabetes From Major Professional Societies[a] (continued)

Category	American Diabetes Association (2025)[14]	American Association of Clinical Endocrinology (2023)[94]	Endocrine Society (older adults, 2019)[95]	American College of Physicians (2024)[96,97]	VA/DoD (US Department of Veterans Affairs /Department of Defense) (2023)[98]	Diabetes Canada (2024)[99]	National Institute for Health and Care Excellence (UK) (2022)[100]	World Health Organization (2018)[101]	International Diabetes Federation (2025)[102]
SGLT2i in those with HF or CKD[c]	Recommended Independent of HbA_{1c} Recommend SGLT2i or GLP-1RA with proven benefit in CKD SGLT2i preferred in HF	Recommended Independent of HbA_{1c} Recommend SGLT2i or GLP-1RA with proven benefit in CKD SGLT2i preferred in HF		Recommended Prioritize adding SGLT2i for CKD or HF	Recommended Independent of HbA_{1c} Recommend SGLT2i with proven benefit in CKD but can also consider GLP-1 RA SGLT2i preferred in HF	Recommended Independent of HbA_{1c} Recommend SGLT2i with proven benefit in CKD but can also consider GLP-1RA SGLT2i preferred in HF	Recommended HF: SGLT2i add to metformin CKD, use SGLT2i if receiving ACEi or ARB or UACR>30 mg/g		Recommended Cardiorenal: GLP-1 RA or SGLT2i (optimal care) Cardiorenal: SGLT2i (basic care) SGLT2i preferred in HF
Combination SGLT2i and GLP-1RA in those with ASCVD or high ASCVD risk	If not at glycemic target	If not at glycemic target			Consider	If not at glycemic target			
When to initiate injectable therapy (ie, GLP-1RA, dual GLP-1/GIP RA, or insulin) to meet glycemic targets	GLP-1RA or dual GLP-1/GIP RA are preferred to insulin for persistent hyperglycemia as initial injectable Consider insulin initially with: Evidence of ongoing catabolism Symptomatic hyperglycemia HbA_{1c} >10% and/or glucose >300 mg/dL	If not at target at <3 mo, GLP-1RA as first injectable; if HbA_{1c} >10% and/or glucose >300 mg/L with symptomatic hyperglycemia, or not at glycemic target, use basal insulin with or without GLP-1RA	Use insulin and sulfonylurea sparingly in older adults			Initiate insulin for symptomatic hyperglycemia and/or metabolic decompensation	Ineffective dual oral therapy: Start NPH Use analogue insulin if hypoglycemia on NPH Start basal bolus or premixed insulin for HbA_{1c}≥9% GLP-1RA for BMI ≥35 or <35 with comorbidities. Stop if HbA_{1c} reduction <1% and weight loss <3% in 6 mo	Start human insulin if goal not achieved on metformin and sulfonylurea; consider long-acting insulin analogues if frequent, severe hypoglycemia on human insulin	Begin insulin therapy when optimized available glucose-lowering medications and lifestyle interventions do not maintain target blood glucose control Commence with single daily injection of basal analog insulin (optimal care) or affordable human, analog, or biosimilar insulin (basic care)
Additional recommendations	Strong weight and comorbidity focus[b]	Strong weight and comorbidity focus[b] Alternate algorithms for "complication-" or "glucose-" centric approaches; focus on rapid goal attainment GLP-1 RA or pioglitazone for stroke	Assess overall health and values to determine treatments and targets; simplify medication and relax targets with cognitive impairment	Do not add DPP-4i to metformin to reduce morbidity or all-cause mortality Discontinue insulin or sulfonylurea when possible; insulin and sulfonylurea are inferior to SGLT2i and GLP-1RA for morbidity and all-cause mortality but "may still have some limited value for glycemic control"	Strong comorbidity focus[b] Deprioritize insulin, sulfonylurea, and meglitinide especially >65 y	Strong comorbidity focus[b] Initial combination therapy with metformin and second agent if. HbA_{1c}>1.5% above target	Second-line: DPP-4i or pioglitazone or sulfonylurea or SGLT2i	Target population is low-resource settings in low- or high-income countries Second line: sulfonylurea If insulin is unsuitable (after metformin and/or sulfonylurea), a DPP-4 inhibitor, SGLT-2i inhibitor, or a thiazolidinedione may be added	Describes 2 levels of standards of diabetes care: "optimal care" sets the standard for evidence based care which would ideally be universally available "basic care" aims to achieve the same objectives but is provided in a healthcare setting with limited resources

Abbreviations: DPP4i, DPP-4 inhibitor; NPH, neutral protamine Hagedorn insulin.

[a] Cells are blank if the topic is not explicitly addressed by the guideline.

[b] Comorbidities include atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and chronic kidney disease (CKD).

[c] Medications with demonstrated cardiovascular or kidney benefit within each class are preferred when used for this indication. For SGLT2i, these include canagliflozin, dapagliflozin and empagliflozin. For GLP-1RA, these include dulaglutide, liraglutide, and semaglutide.

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Heart Failure

Trials of HF outcomes with dapagliflozin and empagliflozin, enrolling up to 50% of participants with type 2 diabetes, report reduction in cardiovascular death and improvement of HF among patients with HF with reduced ejection fraction and HF with preserved ejection fraction, respectively, independent of diabetes status, compared with placebo.[66-69,88] Recent trials of semaglutide and tirzepatide have also reported improved HF symptoms and function in patients with obesity-related HF with preserved ejection fraction compared with placebo.[74,75,109]

Chronic Kidney Disease

SGLT2 inhibitors have beneficial effects on kidney outcomes including reduced progression to kidney failure, eGFR decline to less than 10 to 15 mL/min/1.73 m^2, decrease in eGFR of at least 40%, or death from kidney causes in trials that included people with type 2 diabetes and CKD.[14] The first dedicated kidney outcome trial with a GLP-1RA (injectable semaglutide) demonstrated benefit in reducing major kidney disease events.[110]

Treatment Guidelines and Evidence

Numerous guidelines outline approaches to medical management of hyperglycemia in patients with type 2 diabetes.[14,94-101] Many guidelines recommend an HbA_{1C} target of less than 6.5% or 7% for most nonpregnant adults that is individualized based on patient-related factors, with higher targets (<7.5%-8.5%) for older adults and those with high risk of hypoglycemia or limited life expectancy (Table 4).[14,95,96,102,111] Current guidelines recommend specific SGLT2i agents that improve atherosclerotic cardiovascular disease, HF, CKD, or mortality outcomes and GLP-1RAs that improve atherosclerotic cardiovascular disease, CKD, or mortality outcomes in individuals who have these conditions or are at high cardiovascular risk.[14,94,97-100] Many evidence-based guidelines continue to recommend metformin as first-line treatment,[94-97,99-102] particularly in patients without cardiovascular or kidney comorbidities, although some guidelines no longer state that metformin be used prior to using GLP-1RAs or SGLT2is in patients with atherosclerotic cardiovascular disease, HF, or CKD.[14,94,98] Some guidelines recommend combination SGLT2i and GLP-1RA in patients with type 2 diabetes and cardiovascular disease or those at high risk of CVD if glycemic targets are not met (Table 4). Studies have been limited by small sample sizes in combination therapy subgroups and trials have not consistently shown benefit for the combination of SGLT2is and GLP-1RAs on cardiovascular and kidney outcomes.[73,112]

The major disadvantage of SGLT2is, GLP-1RAs, and dual GIP/GLP-1RAs, aside from their specific adverse effects (Table 2), is limited access in the US due to high cost for individuals without insurance or with high-deductible health plans.[113] Strategies such as co-payment cards, manufacturer patient assistance programs, and the Medicare low-income subsidy may help patients navigate high prescription drug costs.[114] Generic formulations of liraglutide and dapagliflozin have been approved in the US, but are not widely available.

Intensification of Therapy

Type 2 diabetes is a progressive disease and combination pharmacotherapy is often required in a stepwise manner to maintain HbA_{1C} goals. When intensifying the glucose-lowering regimen, it is important to consider other drug- and patient-specific factors (Table 2).[91,115] When making decisions about additional therapy, a patient-centered approach that addresses patient priorities and preferences while establishing attainable goals is beneficial.[14,116,117] Although many patients with type 2 diabetes eventually require insulin due to progressive hyperglycemia, insulin may be associated with hypoglycemia. The risk of hypoglycemia is highest in patients taking insulin or secretagogues (ie, sulfonylureas or meglitinides; Table 2) who are 75 years or older or have cognitive impairment, CKD, or insulin deficiency.[118-120] In a population-based study of 1.66 million people filling at least 1 glucose-lowering medication prescription, the rate of severe hypoglycemia per 100 person-years was 2.3 for people 75 years and older, 1.3 for those aged 64 to 75 years, and 0.9 for younger ages.[121] Sulfonylureas are inexpensive and have high HbA_{1C}-lowering efficacy.[38,81] Reducing the risk of hypoglycemia with sulfonylureas can be achieved by only taking the medication when eating and using the lowest effective doses. For those at higher risk of hypoglycemia, long-acting glyburide should be avoided, and all other sulfonylureas should be used cautiously.[55,56,59,92] In patients already treated with insulin and/or insulin secretagogues such as sulfonylureas or meglitinides (Table 3) for whom addition of a SGLT2i or GLP-1RA is indicated, deintensification (dose reduction or discontinuation) of existing therapy may be considered to minimize hypoglycemia risk.[14,122]

Metabolic Surgery

Metabolic (bariatric) surgery referral may be considered in people with type 2 diabetes who have a body mass index greater than or equal to 30.0 (or greater than or equal to 27.5 in Asian individuals), especially in the presence of other obesity-related comorbidities such as hypertension or dyslipidemia. In addition to weight reduction and decreased glycemia (with diabetes remission in some patients), expected benefits of metabolic surgery include improved quality of life, reduced cardiovascular events, and decreased risk of hepatocellular, colorectal, pancreatic, gallbladder, breast, endometrial, and ovarian cancers.[14,123-126]

Practical Considerations

Patients with type 2 diabetes are commonly treated by primary care clinicians. HbA_{1C} should be assessed at least every 6 months or every 3 months for patients not meeting their glycemic targets or for those with recent glucose-lowering medication dose adjustments. Referrals to a diabetes care and education specialist for diabetes self-management education and to a registered dietitian for medical nutrition therapy are recommended for all individuals with type 2 diabetes.[14] Most adults with type 2 diabetes should be counseled to engage in moderate- to vigorous-intensity aerobic physical activity such as brisk walking, swimming, or running (≥150 minutes/week) and resistance exercise (2-3 sessions/week). Patients should be counseled to lose weight or maintain weight if weight loss is not advisable. Multidrug regimens, complicated insulin regimens (ie, multiple daily injections), high-dose insulin (ie, >200 units/d), and consideration of use of diabetes technology (such as CGMs or insulin pumps) may warrant consultation with endocrinology. Lack of expected response to treatment or persistent hyperglycemia in patients with new-onset diabetes who are adherent to metformin or other oral glucose-lowering therapy should prompt screening for type 1 diabetes with islet autoantibodies (eg, glutamic acid

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decarboxylase) or other types of diabetes (Table 1) and may necessitate endocrine referral.

Limitations

This review has several limitations. First, it is not a systematic review, and the quality of included literature was not formally evaluated. Second, relevant articles may have been missed. Third, randomized clinical trials investigating cardiovascular outcomes did not generally include individuals at lower risk of cardiovascular disease. Fourth, clinical trials of newer glucose-lowering drugs such as SGLT2is and GLP1RAs were of relatively short duration, and long-term effects of these medications are currently unknown.

Conclusions

Type 2 diabetes affects up to 14% of the global population and is associated with preventable long-term complications such as cardiovascular disease, kidney failure, vision loss and increased mortality. In addition to lifestyle modifications including diet, exercise and weight management, metformin is generally first-line therapy for attainment of HbA_{1C} targets. For individuals with type 2 diabetes and cardiovascular or kidney disease or at high cardiovascular risk, guidelines recommend early treatment with SGLT2i and/or GLP-1RA medications.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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